Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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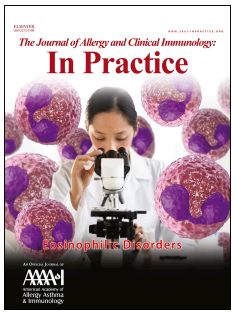

SARS-Cov-2 infection in severe asthma patients treated with biologics

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SARS-Cov-2 infection in severe asthma patients treated with biologics

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Conflict of interest

AIP has received honoraria from AstraZeneca, GlaxoSmithKlein, Novartis, Boehringer Ingelheim, Chiesi, and ELPEN. EF has received honoraria from AstraZeneca, GlaxoSmithKlein, Novartis, Boehringer Ingelheim, Chiesi, ELPEN and Roche. NT has received honoraria for presentations and consultancy fees from AstraZeneca, Boehringer Ingelheim, Chiesi, ELPEN, GSK, Menarini, Novartis and Sanofi Specialty Therapeutics. KA has received honoraria fees, research grants, travel grants from GSK, Astra-Zeneca,

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Abstract

Background: At the beginning of the pandemic, there have been considerable concerns regarding COVID-19 severity and outcomes in severe asthma patients treated with biologics.

Objective: To prospectively observe a cohort of severe asthmatics treated with biologics for the risk of SARS-CoV-2 infection and disease severity during COVID-19 pandemic.

Methods: Physicians from centers treating severe asthma patients all over Greece provided demographic and medical data regarding their patients treated with biologics. Physicians were also asked to follow up patients during the pandemic and to perform a PCR test in case of a suspected SARS-Cov-2 infection.

Results: Among the 591 severe asthmatics (63.5% female) included in the study, 219(37.1%) were treated with omalizumab, 358(60.6%) with mepolizumab and 14(2.4%) with benralizumab. In total, 26 patients (4.4%) had a confirmed SARS-CoV-2 infection, 9 (34.6%) of whom were admitted to the hospital due to severe COVID-19, and one required mechanical ventilation and died 19 days after admission. Out of the 26 infected patients, 5(19.2%) experienced asthma control deterioration, characterized as exacerbation that required treatment with systemic corticosteroids. The scheduled administration of the biological therapy was performed timely in all patients with the exception of two, in whom it was postponed for one week according to their doctors' suggestion.

Conclusion: Our study confirms that despite the initial concerns, SARS-CoV-2 infection is not more common in asthmatics treated with biologics compared

to the general population, while the use of biologic treatments for severe asthma during the COVID-19 pandemic does not seem to be related to adverse outcomes from severe COVID-19.

Highlights box

What is already known about this topic

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to cause significant morbidity and mortality all over the world. Previous studies have provided evidence that COVID-19 in severe asthmatics receiving different types of biological treatments is not associated with greater risk of hospitalization, ICU admission or death

What does this article add to our knowledge?

Our study confirms that the use of biologics for the treatment of severe asthma is safe during the pandemic and despite the initial concerns COVID-19 is not more common in asthmatics treated with biologics compared to general population.

How does this study impact current management guidelines

Administration of biologics is not necessary to be postponed due to SARS-CoV-2 infection

Abbreviations

ACE2: Angiotensin-Converting Enzyme 2

ARDS: Acute Respiratory Distress Syndrome

COVID-19: Coronavirus Disease 2019

ICU: Intensive Care Unit

IgE: Immunoglobulin-E

LAMAs: Long-Acting Muscarinic Antagonists

pDCs: plasmacytoid dendritic cells

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

Key words.

Severe asthma

COVID-19

Biologics

Mepolizumab

Omalizumab

Benralizumab

Exacerbation

SARS-CoV-2

Introduction

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], continues to cause significant morbidity and mortality all over the world. The natural history of COVID-19 is characterized by three main phases, with different symptoms ranging from asymptomatic or mild disease to acute respiratory distress syndrome (ARDS) with multiorgan failure and shock [2]. The commonest cause of death in patients with severe COVID-19 is associated with lung involvement [3] and this is probably the reason why, in the beginning of the pandemic, respiratory diseases, including asthma, have been considered as potent risk factors for severe disease. Furthermore, since respiratory viral infections have been well recognized as risk factors for asthma exacerbations [4, 5], it was initially hypothesized that SARS-CoV-2 infection would also act as an exacerbation trigger, however, up-to-date, relevant published reports studying asthmatic patients have provided controversial results on whether asthmatic patients are at increased risk of experiencing more severe disease [6-13]. Similarly, although an early study has shown poor outcomes after SARS-CoV-2 infection in patients with severe asthma treated with biologics, [7], several further case reports [14-19] as well as recent studies in large cohorts, [20, 21] have provided evidence that COVID-19 in severe asthmatics receiving different types of biological treatments is not associated with greater risk of hospitalization, ICU admission or death.

In this multicentered study, we aimed to prospectively observe a cohort of severe asthmatics treated with biologics for the risk of SARS-CoV-2

infection, and COVID-19 severity and outcome and to assess any differences in all above with respect to the different biological treatments administered.

Methods

Study design

On March 2020, once the first COVID-19 cases were reported in Greece, respiratory physicians all over the country, involved in the treatment of severe asthmatic patients, were called to provide data of their patients currently being treated with biologics in their outpatient clinics and offices. Eligible patients should be over 18 years old, had a confirmed diagnosis of severe asthma according to ERS/ATS criteria [22] and should being currently treated with biologics for at least 4 months, according to 2020 GINA Guidelines [23]. Exclusion criteria included refusal of the patient to participate in the study, non-adherence to treatment, and drug interruption for any reason (apart from treatment been postponed due to COVID-19 according to the physician's decision). Physicians were also asked to prospectively follow up their patients, to contact them regularly, and to perform molecular tests for SARS-CoV-2 in case a patient presented any suspicious symptoms. Patients were also asked to contact their treating physicians in case they experience any relevant symptoms. All cases found positive for SARS-CoV-2 infection were recorded and data on asthma deterioration as well as disease severity and outcomes were also prospectively collected. All patients were prospectively followed up to April 2021 when vaccination was initiated for severe asthma patients.

Data collection

In all patients, demographic characteristics, disease duration, FEV_1 (measured during the previous 6 months) and treatments for asthma (including inhaled therapies and oral corticosteroids use) were recorded. Furthermore, data on the type of biologic therapy and treatment duration were also recorded. In every case the patient experienced suspicious symptoms of SARS-CoV-2 infection (such as such as fever, cough, tiredness, loss of taste or smell, sore throat, headache, aches and pains, diarrhea, difficulty breathing or shortness of breath, chest pain, loss of speech or mobility and confusion) a PCR test was performed and in cases SARS-CoV-2 infection was documented the physicians were asked to provide data regarding disease severity, need for hospital and/or ICU admission, occurrence of symptoms suggesting an asthma exacerbation, medication postponement due to SARS-CoV-2 and the outcome of the patient. Asthma exacerbation was defined as deterioration of asthma symptoms (i.e. dyspnea, cough, wheezing and/or chest tightness), which required increase in the use of bronchodilators together with treatment with antibiotics and/or systemic corticosteroids [23]. For patients who were admitted to the hospital, information regarding the presence of SARS-CoV-2 related pneumonia, duration of hospital stay, need for mechanical ventilation and/or ICU admission and the patient's outcome were also provided by the treating physician. The study protocol was approved by the local Ethics Committee of "Attikon" University Hospital, and all patients provided their consent to be included in the database.

Statistical analysis

Categorical variables are presented as n (%), whereas numerical variables are presented as mean ± standard deviation (SD) or median (interquartile ranges) for normally distributed and skewed data, respectively. Normality of distributions was checked with Kolmogorov-Smirnov test. Comparisons of variables between groups were performed using Mann-Whitney U-test and Kruskal-Wallis test, as appropriate. Statistical significance was established at $p<0.05$. Data were analyzed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

23 asthma clinics from Greece provided data of 591 severe asthmatic patients treated with biologics. The mean age of the patients was 57± 14 years, 63.5% of included subjects were female. Mean asthma duration was 24 ± 14 years. From the patients included in the study, 219 patients (37.1%) were receiving omalizumab, while 358 (60.6%) and 14 (2.4%) patients were receiving mepolizumab and benralizumab, respectively. The low number for benralizumab treated patients was attributed to a late release of the drug in Greece according to regulatory authorities. 305 (51.5%) of patients were atopic. Patients receiving omalizumab were as expected atopic while among those receiving mepolizumab and benralizumab atopy was present in 22.9% and 28.6% respectively. The mean duration of therapy with biologics was 36±13 months. A SARS-CoV-2 infection was documented in 26 (4.4%) patients, 9 (34.6%) of whom required hospitalization for severe COVID-19. Concerning patients' characteristics, mepolizumab recipients were significantly older, while those who were administered omalizumab had a longer asthma duration, received less frequently long-acting muscarinic antagonists (LAMAs) and were on biologic therapy for a significantly longer period of time. Demographic and functional characteristics of the study participants is shown comprehensively in Table 1.

Comparison of patients according to SARS-CoV-2 infection, type of biological treatment and requirement of hospital admission

Patients infected from SARS-CoV-2 were receiving biologic therapy for a shorter period of time (months) compared to those not infected i.e., median (IQR): [12.0 (7.0, 25.0) versus 28.0 (14.0, 41.0), p<0.001]. No other differences were observed between these two groups of patients, as shown in Table 2.

Among the 26 patients experiencing COVID-19, omalizumab had been administered in 9 (34.6%) patients, while 16 (61.5%) had been receiving mepolizumab and 1 (3.9%) patient had been receiving benralizumab. COVID-19 patients receiving omalizumab were mainly male and were more often receiving oral corticosteroids, in contrast to patients receiving the other two types of biologics.

Nine patients required hospital admission due to COVID-19, with most of them being female, 8 out of 9 patients (88.8%). All hospitalized patients had clinical and radiological manifestations of pneumonia. Asthma duration (years) was significantly longer in patients who required hospitalization compared to those who did not [median IQR 35.0 (23.5, 41.0) versus 10.0 (6.5, 25.5), p=0.009]. Finally, hospitalized patients were more frequently receiving LAMAs (77.8% versus 35.5%, for patients requiring and not requiring hospital admission, respectively, p=0.039). Interestingly, all patients requiring hospital admission were on treatment with mepolizumab, and one patient in this group was admitted and died in the ICU due to COVID-19 complications.

Finally, there was no difference in atopic status between patients infected and not infected from COVID 19 and those who required hospitalization due to–severe COVID-19 compared to those who were not

hospitalized. Comparisons of patients infected from SARS-CoV-2 according to the type of biological treatment and requirement of hospital admission are presented on Table 3 and Table 4, respectively.

Asthma exacerbations and biologic administration during SARS-CoV-2 infection

Among patients infected from SARS-CoV-2, biologic treatment administration was delayed for 7 days in two patients, both of them on therapy with mepolizumab according to their treating physicians personal decision, since there was no official guideline for such a practice. The first case concerned a 71-year-old male patient who had clinical symptoms of asthma exacerbation (defined as asthma control deterioration requiring treatment with systemic corticosteroids). and who also required hospital admission and supplemental oxygen administration due to COVID-19 pneumonia. The second case regarded a 58-year-old female patient who also had symptoms of asthma exacerbation but did not require hospital admission. In all other infected patients, the dose of the biologic was administered in their scheduled time, while it is important to mention that 2 of the hospitalized patients received their dose during hospital stay timely and without any complication. From the patients who experienced symptoms of asthma exacerbations, only one was using nasal corticosteroids, and this patient did not require hospital admission.

Finally, except from the two aforementioned patients, three more patients (in total five of PCR+ patients, 19.2%) experienced an asthma exacerbation, however, no hospital admission was required.

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Discussion

In our study we have shown that treatment with biologics was not associated with an increased risk of SARS-Cov-2 infection compared to the general population. However, once infected, these patients seem to be at greater risk of hospital admission due to COVID-19 complications, while some also seem to lose asthma control and to experience symptoms of an asthma exacerbation. From the clinical experience in our country, we suggest that the scheduled dose of the biologic therapy could be administered on time, regardless of SARS-Cov-2 infection, as such a practice does not seem to result in adverse outcomes. Finally, all patients admitted to the hospital were under treatment with mepolizumab.

In our study we showed that 26/591 patients (4.4%) in our cohort had a SARS-CoV-2 infection during the first 14 months of the pandemic, a prevalence which is in line with the estimated prevalence of COVID-19 in Greece at that time period (which varied between 1.9% and 6.01% depending on the season and lock-down imposition). Our findings are in accordance to previous studies showing a lower probability of the disease among asthmatics compared to the general population [10, 20, 21, 24, 25], suggesting that severe asthmatics treated with biologics are not at higher risk of getting infected. Potential reasons for this observation might include, self-protection measures such as social distancing, lockdown restrictions, and hygiene rules, mainly due to awareness of viruses acting as a trigger for exacerbations [26, 27]. Another possible explanation is that the use of biological therapies results in better asthma control in patients with severe disease, thus avoiding the chronic or recurrent use of systemic corticosteroids, which is a predisposal

377 factor for SARS-CoV-2 infection, due to decreased innate and acquired
378 immunity [20]. Furthermore, it has been hypothesized that inhaled
379 corticosteroids might also prevent or mitigate the development of
380 coronaviruses infections and thus, asthmatic patients treated with high doses
381 of ICS (like those included in our cohort) may have been protected from
382 severe SARS-CoV-2 infection [6, 28-30]. Finally, it has been proposed that
383 also mucus hypersecretion which often exists in severe asthmatics, could
384 possibly prevent distal viral penetration [11].

385 Previous studies, including various reports from different regions have
386 shown that underlying asthma is reported to account for 0.9-17% of
387 hospitalized patients with COVID-19 [31, 32] and that asthma severity seem
388 to influence the duration of hospitalization since asthmatic patients treated in
389 step 5 showed significant prolonged admission duration than those with step 1
390 [6]. In our cohort of severe asthmatics treated with biologics, 9 out of the 26
391 infected patients (34.6%) required hospital admission, an incidence that is
392 much greater that those reported from other severe asthma registries [24, 33],
393 however the data on severe asthma and COVID-19 are scarce. Furthermore,
394 since we have not evaluated significant differences in the baseline
395 characteristics between patients who required hospital admission and those
396 who did not, further research is needed to recognize the patients who are at
397 greater risk for more severe COVID-19**.** In our cohort, only one patient, a 66-
398 year-old woman with severe obesity (BMI:40.2kg/m^2) and cardiovascular
399 comorbidities, was admitted in the ICU and finally died from COVID-19
400 complications, an observation that is also in accordance to previous reports in

401 which the worst outcomes were observed mainly in patients with major
402 comorbidities [10, 21].

403 The role of eosinophils in the host defense against viral infection has
404 been widely described [34]. In severe COVID-19 patients, Th2 immune
405 response is stimulated and eosinophils may play a central role in precipitating
406 immune derangement and aggravating SARSCoV-2-induced pneumonia [35].
407 At the beginning of the infection, an active migration of circulating eosinophils
408 from the peripheral blood to target tissues occurs, followed by a decrease in
409 the number or peripheral eosinophils [34]. Furthermore, an elevation in the
410 eosinophils stimulating cytokines, such as IL-5 and GM-CSF has been also
411 described [36]. Several laboratory reports of patients with severe COVID-19
412 have described a lower number or peripheral eosinophils compared to non-
413 severe cases [37-41] while a retrospective study by has suggested that
414 preexisting eosinophil count greater than or equal to 150/mL was protective
415 from future COVID-19–associated hospitalization [42]. Interestingly, in our
416 cohort, all patients who were admitted to the hospital were receiving
417 mepolizumab. This association might be related to the eosinophil depletion
418 caused by this biologic, which according to the aforementioned studies, might
419 predispose to more severe disease[43]. Our observation is in accordance to a
420 previous report from the Dutch Severe Asthma Registry in which 6 out of 7
421 patients who required hospital admission for COVID-19 were treated with anti
422 -IL-5 therapy, and three of them required admission in an ICU [7]. However
423 we have to admit that patients on the mepolizumab group were older and the
424 one patient who died was obese and had severe comorbidities (obesity,
425 diabetes and cardiovascular disease) which is in accordance with the

aforementioned Dutch cohort in which also the one deceased patient had obesity and diabetes [7].

Five out of the 26 SARS-CoV-2 infected patients in our cohort experienced symptoms of exacerbation during infection, two of them being hospitalized due to COVID-19 pneumonia, while the remaining three did not require hospital admission, neither for COVID-19 nor for the asthmatic exacerbation. This finding comes in contrast with reports from previous studies suggesting that SARS-CoV-2 is not a cause of asthma exacerbations [33], however, as the number of exacerbating patients in our study is small, and the management of exacerbations was based on the by-phone evaluation of patients by the treating physician, the potential of overtreatment with systemic corticosteroids cannot be excluded.

In our study, none of the patients receiving omalizumab required hospital admission after SARS-CoV-2 infection. It has been described that respiratory allergies and allergen exposures are associated with significant reduction in angiotensin-converting enzyme 2 (ACE2) expression, which is the cellular receptor for SARS-CoV-2 [44] and thus the virus cannot easily penetrate the respiratory system. Furthermore, although in allergic subjects, IgE receptor cross-linking on plasmacytoid dendritic cells (pDCs) suppresses the anti-viral activity of pDCs [45], when these patients are treated with omalizumab, the blockage of the circulating IgE leads to a long-lasting reduction of its production and a decrease on the expression of IgE receptors on pDCs, a phenomenon that might generally strengthen the anti-viral immune responses [46]. In this regard, the presence of atopy in combination with omalizumab therapy might have exhibited a somehow protective role

against severe COVID-19. On the other hand, non-allergic asthma patients are usually older, and comorbidities such as obesity and diabetes, due to chronic subclinical inflammation as well as chronic systemic corticosteroid use are more often, making these patients more vulnerable to severe COVID-19 [47]. “However, although no significant difference was observed between patients who required hospitalization because of severe COVID-19 compared to those who were not hospitalized, the small number of infected patients and the even smaller number of patients who required hospital admission cannot lead to safe conclusions”.

In our cohort only two patients did not receive their scheduled dose of biologic during SARS-CoV-2 infection on time (they both received it 7 days later). Although there is no official guideline on whether the biologic treatment should be postponed during SARS-CoV-2 infection, it has been suggested that treatments with biologics during the COVID-19 pandemic appear to be safe and can be administered normally, but should be interrupted in cases of confirmed SARS-CoV-2 infection [48]. At the time of the design of our study, the aforementioned recommendation did not exist and the treating physician was free to decide whether to postpone or not the biologic administration and, in most cases, scheduled administration was decided even in patients who were hospitalized for severe COVID-19. Although we must admit that our data are limited and our study does not include a control arm it seems that these decisions did not lead to adverse outcomes. Moreover, in our opinion, this strategy might have contributed in maintenance of asthma control during SARS-CoV-2 infection in most patients.

Our study has several limitations. First, molecular tests were performed only in symptomatic patients. According to that, it is possible that a number of patients who were infected but were completely asymptomatic may have not been detected and thus were not included in the study. However, the treating physician were instructed to perform PCR tests in any patient with symptoms suggestive of SARS-CoV-2 infection and all patients reported as COVID-19 cases had a confirmed diagnosis. On the other hand, one advantage of our study is that all patients with symptoms had a molecular diagnosis of SARS-CoV-2 infection and diagnosis was not based only on suggestive symptoms. A second limitation is that only a minority of patients were receiving benralizumab. The reason for that is that benralizumab therapy was not yet approved in our country during the study period and the few patients receiving such treatment were those who received the antibody through a pre-approval access program. However, we have decided to include those patients in order to have a more general picture of the outcomes of SARS-CoV-2 infection in patients with severe asthma treated with biologics. Furthermore, although results have not been checked for possible confounders, -demographic or clinical- that could be driving the conclusions as has been shown in previous studies [49, 50] the prospective design of the study provides a general picture of the risk of severe asthmatics treated with biologics regarding the risk of SARS CoV-2 infection and the infection outcome. Finally, in accordance with previous studies, we have also shown that treatment with biologics in patients with severe asthma does not seem to be related to adverse outcomes from severe COVID-19. However, their possible protective role against adverse COVID-19 outcomes cannot be documented by the data of this study".

In conclusion, our study confirms that the use of biologics for the treatment of severe asthma is safe during the pandemic and despite the initial concerns COVID-19 is not more common in asthmatics treated with biologics compared to general population. We believe that It would be interesting to study the outcomes of the same cohort of patients during the vaccination period, when a high coverage of this vulnerable population has been achieved. Although some patients have experienced symptoms of asthma exacerbation during COVID-19, in the great majority, infection did not result in loss of control and scheduled administration of biologics was not interrupted. Clinicians should follow the current guidelines regarding the treatment of severe asthmatics and retain a close monitoring of the infected patients, in order to timely recognize those with more severe COVID-19 who will require hospital admission and special care.

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Table 1 Demographic and functional characteristics of the study participants according to the use of biological therapy

Variable	**All** **N=591**	**Omalizumab** **N=219**	**Mepolizumab** **N=358**	**Benralizumab** **N=14**	**p-value**
Age (years)	57.0 (47.0, 68.8)	55.0 (46.0, 64.0)	60.0 (50.0, 69.0)	43.0 (37.0, 49.7)	**<0.001**
Gender (female) N (%)	386 (65.3)	130 (59.4)	247 (69.0)	9 (64.3)	0.062
Smoking status (current smokers) N (%)	128 (21.7)	36 (16.4)	87 (24.3)	5 (35.7)	0.131
Pack years	0.0 (0.0, 11.0)	0.0 (0.0, 10.0)	0.0 (0.0, 13.0)	5.0 (0.0, 15.0)	0.312
BMI (kg/m^2)	27.4 (24.6, 32.0)	27.0 (25.0, 32.0)	27.0 (24.6, 32.4)	23.7 (22.0, 30.7)	0.241
FEV_1* (%pred)	76.0 (64.7, 90.2)	74.0 (64.0, 91.0)	78.0 (64.5, 90.0)	77.0 (64.8, 98.0)	0.870
Asthma duration (years)	22.0 (12.0, 34.0)	24.0 (15.0, 37.0)	20.0 (10.0, 31,3)	13.0 (6.0, 26.3)	**<0.001**
Asthma treatment N (%) **LABA**	360 (60.9)	134 (61.2)	217 (60.6)	9 (64.3)	0.914

LAMA	285 (48.2)	81 (37.0)	197 (55.0)	7 (50.0)	**<0.001**
LTRA	214 (36.2)	82 (37.4)	126 (35.2)	6 (42.9)	0.571
ICS	591 (100)	219 (100)	358 (100)	14 (100)	1.000
High ICS dose⁺ N (%)	542 (91.7)	191 (87.2)	337 (94.1)	14 (100)	**0.007**
Use of nasal corticosteroids N (%)	151 (25.5)	73 (33.3)	77 (21.5)	1 (7.1)	**0.005**
Atopy N (%)	305 (51.6)	219 (100)	82 (22.9)	4 (28.6)	**<0.001**
Duration of treatment with biologics (months)	27.0 (13.0, 40.0)	38.0 (13.0, 94.0)	24.0 (15.0, 36.0)	12.0 (9.7, 17.3)	**<0.001**
OCS maintenance therapy	106 (17.9)	40 (18.3)	62 (17.3)	4 (28.6)	0.553
OCS dose (mg of prednisolone or equivalent)	5.0 (5.0, 10.0)	5.0 (5.0, 10.0)	5.0 (2.5, 10.0)	3.8 (2.5, 5.0)	0.167
SARS-CoV-2 infected N (%)	26 (4.4)	9 (4.1)	16 (4.5)	1 (7.1)	0.861
Hospitalization for COVID-19 N (%)	9 (1.5)	-	9 (2.5)	0 (0.0)	N/A

Duration of hospital stay (days)	13.5 (4.3, 19.8)	-	13.5 (4.3, 19.8)	-	N/A
ICU admission for COVID-19 N (%)	1 (0.2)	-	1 (6.2%)	-	N/A
Death from COVID-19 N (%)	1 (0.2)	-	1 (6.2%)	-	N/A

Data are presented as N (%) or median (IQR) unless otherwise indicated

Abbreviations: BMI: Body mass Index, FEV_1: Forced Expiratory Volume in one second, LABA: Long Acting beta agonists, LAMA: Long acting muscarinic antagonists, LTRA: Leukotriene receptor antagonists, ICS: inhaled corticosteroids,, OCS : Oral corticosteroids, ICU: Intensive Care Unit.

*FEV_1 measure was performed in the last 6 months prior to inclusion to the database.

$^{+}$ ICS dose was calculated according to the GINA report dosing tables.

Table 2

Comparison of patients experiencing and not experiencing SARS-CoV-2 infection

Variable	**Patients with SARS-CoV-2 infection N=26**	**Patients without SARS-CoV-2 infection N=565**	**p-value**
Age	55.5 (46.7, 66.5)	58.8 (47.0, 68.0)	0.725
Gender	15 (57.7)	371 (65.7)	0.404
Smoking status (current smokers)	8 (30.8)	120 (21.2)	0.307
Pack-years	0.0 (0.0, 12.5)	0.0 (0.0, 11.3)	0.941
BMI (kg/m^2)	26.0 (24.6, 30.7)	27.5 (24.6, 32.0)	0.313
FEV_1 (%pred)	75.2 (61.9, 87.5)	76.0 (65.0, 90.9)	0.506
Asthma duration (years)	23.0 (7.7, 36.3)	22.0 (12.0, 34.0)	0.620

Type treatment with biologic **Omalizumab** **Mepolizumab** **Benralizumab**	 9 (34.6) 16 (61.5) 1 (3.8)	 210 (37.2) 342 (60.5) 13 (2.3)	0.861
Duration of treatment with biologics	12.0 (7.0, 25.0)	28.0 (14.0, 31.0)	**<0.001**
High ICS dose^{+} N (%)	24 (92.3)	518 (91.7)	0.910
Use of nasal corticosteroids N (%)	7 (26.9)	144 (25.5)	0.954
Atopy N (%)	10 (38.5)	295 (52.2)	0.078
OCS maintenance therapy	3 (11.5)	103 (18.2)	0.385
OCS dose (mg of prednisolone or equivalent)	5.0 (5.0, 5.0)	5.0 (5.0, 10.0)	0.650

Data are presented as N (%), or median (IQR) unless otherwise indicated

Abbreviations: BMI: Body mass Index, FEV_1: Forced Expiratory Volume in one second, OCS: Oral corticosteroids

Bold indicates statistically significant differences

[+] ICS dose was calculated according to the GINA report dosing tables.

Table 3 Comparison of patients experiencing SARS-CoV-2 infection according to the type of biologic

Variable	**Omalizumab SARS-CoV-2 infected N=9**	**Mepolizumab SARS-CoV-2 infected N=16**	**Benralizumab SARS-CoV-2 infected N=1**	**p-value**
Age (years)	55.0 (40.0, 65.0)	57.5 (48.5, 70.3)	52.0	0.416
Gender (female) N (%)	2 (22.2)	12 (75.0)	1 (100)	**0.026**
Smoking status (current smokers) N (%)	1 (11.1)	7 (43.8)	1 (100)	0.188
Pack years	0.0 (0.0, 3.8)	2.5 (0.0, 21.5)	0.0	0.295
BMI (kg/m^2)	26.0 (25.5, 30.7)	25.3 (24.6, 33.9)	20.0	0.297
FEV_1 (%pred)	77.0 (66.4, 99.5)	74.1 (55.0, 82.0)	89.0	0.279
Asthma duration (years)	23.0 (10.0, 33.0)	26.5 (7.3, 38.8)	6.0	0.439
Duration of treatment with biologics(months)	11.0 (7.0, 13.0)	15.5 (9.3, 34.0)	6.0	0.109
High ICS dose$^+$ N (%)	8 (88.9)	15 (93.8)	1 (100)	0.870

Use of nasal corticosteroids N (%)	2 (22.2)	5 (31.3)	0 (0%)	0.692
Atopy N (%)	9 (100)	1 (6.3)	0 (0%)	<0.001
OCS maintenance therapy	1 (11.1)	1 (6.3)	1 (100)	**0.017**
OCS dose (mg of prednisolone or equivalent)	5.0 (5.0, 5.0)	5.0 (5.0, 5.0)	5.0	1.000
Hospitalization for COVID-19 N (%)	0 (0.0)	9 (56.3)	0 (0.0)	N/A
Duration of hospital stay (days)	N/A	13.5 (4.3, 19.8)	N/A	N/A
ICU admission for COVID-19 N (%)	0 (0.0)	1 (6.2%)	0 (0.0)	N/A
Death from COVID-19 N (%)	0 (0.0)	1 (6.2%)	0 (0.0)	N/A

Data are presented as N (%), or median (IQR) unless otherwise indicated

Abbreviations: BMI: Body mass Index, FEV_1: Forced Expiratory Volume in one second, OCS: Oral corticosteroids

Bold indicates statistically significant differences

[+] ICS dose was calculated according to the GINA report dosing tables.

Table 4

Comparison of patients infected from SARS-CoV-2 according to the requirement of hospital admission

Variable	**Infected patients requiring hospital admission N=9**	**Infected patients not requiring hospital admission N=17**	**p-value**
Age (years)	55.0 (51.0, 71.0)	56.0 (46.0, 65.5)	0.458
Gender (female) N (%)	8 (88.8)	7 (41.2)	**0.019**
Smoking status (current smokers) N (%)	4 (44.4)	4 (23.5)	0.272
Pack years	5.0 (0.0, 20.0)	0.0 (0.0, 11.3)	0.488
BMI (kg/m^2)	24.6 (24.4, 33.7)	26.0 (25.0, 30.7)	0.628
FEV_1 (%pred)	65.0 (47.5, 84.0)	76.1 (64.6, 90.5)	0.388
Asthma duration (years)	35.0 (23.5, 41.0)	10.0 (6.5, 25.5)	**0.009**

Asthma treatment N (%)			
LABA	7 (77.8)	12 (70.6)	0.694
LAMA	7 (77.8)	6 (35.3)	**0.039**
LTRA	5 (55.6)	4 (23.5)	0.102
ICS	9 (100)	17 (100)	1.000
High ICS dose [+]	9 (100)	15 (88.2)	0.284
Use of nasal corticosteroids N (%)	3 (33.3)	4 (23.5)	0.419
Atopy N (%)	1 (11.1)	9 (52.9)	0.097
Duration of treatment with biologics(months)	19.0 (11.0, 36.5)	11.0 (7.0, 18.0)	0.075
Type treatment with biologic			**0.014**
Omalizumab	0 (0.0)	9 (52.9)	
Mepolizumab	9 (100)	7 (41.2)	
Benralizumab	0 (0.0)	1 (5.9)	
OCS maintenance therapy	1 (11.1)	2 (11.8)	0.960

OCS dose (mg of prednisolone or equivalent)	5.0 (5.0, 5.0)	5.0 (5.0, 5.0)	1.000

Data are presented as N (%), or median (IQR) unless otherwise indicated

Abbreviations: BMI: Body mass Index, FEV_1: Forced Expiratory Volume in one second, LABA: Long Acting beta agonists, LAMA: Long acting muscarinic antagonists, LTRA: Leukotriene receptor antagonists, ICS: inhaled corticosteroids,, OCS : Oral corticosteroids, ICU: Intensive Care Unit.

[+] ICS dose was calculated according to the GINA report dosing tables.